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<p>(21) International Application Number: PCT/HU91/00053 (22) International Filing Date: 20 December 1991 (20.12.91) (30) Priority data: 8397/90 21 December 1990 (21.12.90) HU (71) Applicant (for all designated States except US): GYÓGYSZERKUTATÓ INTÉZET K.V. [HU/HU]; Szabadságarcosok útja 47-49, H-1045 Budapest (HU). (72) Inventors; and (75) Inventors/Applicants (for US only) : ANDRÁSI, Ferenc [HU/HU]; Kútvölgyi út 69, H-1125 Budapest (HU). BERZSENYI, Pál [HU/HU]; Buljovszky u. 12, H-1174 Budapest (HU). BÓTKA, Péter [HU/HU]; Harrer P. u. 18, H-1033 Budapest (HU). GOLDSCHMIDTNE, Horváth, Katalin [HU/HU]; Alsóhegy u. 28, H-1118 Budapest (HU). HÁMORI, Tamás [HU/HU]; Amfiteátrum u. 27, H-1031 Budapest (HU). KÖRÖSI, Jenő [HU/HU]; Attila u. 27, H-1013 Budapest (HU). MORAVCSIK, Imre [HU/HU]; Mester u. 38, H-1095 Budapest (HU). SZIRAKI, István [HU/HU]; Báthory u. 12, H-1054 Budapest (HU).</p>		<p>(74) Agent: DANUBIA; V. Bajcsy Zs. u. 16, H-Budapest (HU). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, PL, SE (European patent), SU*, US. Published With international search report.</p>
<p>(54) Title: 1-(4-ACYLAMINOPHENYL)-7,8-METHYLENEDIOXY-5H-2,3-BENZO-DIAZEPINE DERIVATIVES AND ACID ADDITION SALTS THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME</p>		
<div style="text-align: center;"> <p>(I)</p> </div>		
<p>(57) Abstract</p> <p>The invention relates to novel compounds of general formula (I), wherein R stands for hydrogen or a C₁₋₄ alkyl group optionally substituted by a carboxyl or C₂₋₅ alkoxy-carbonyl group; and R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl group, and the stereoisomers as well as acid-addition salts of these compounds. The invention also relates to pharmaceutical compositions containing the above compounds as well as to a process for the preparation of the novel compounds of general formula (I). The compounds of the invention possess central nervous system effects, more particularly antidepressive and antiparkinsonian action. They are non-mutagenic in the Ames test. Thus, they can be useful for the treatment of depressive illnesses and parkinsonism.</p>		

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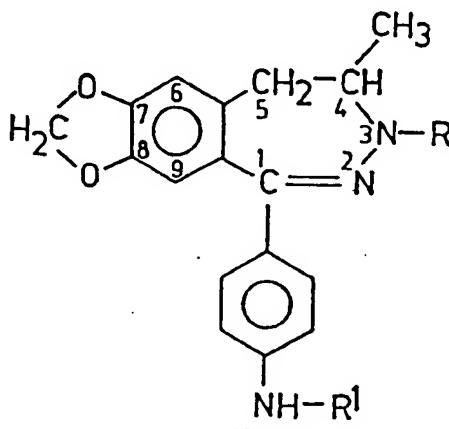
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1-(4-ACYLAMINOPHENYL)-7,8-METHYLENEDIOXY-5H-2,3-BENZO-
DIAZEPINE DERIVATIVES AND ACID ADDITION SALTS THEREOF,
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR
PREPARING SAME

5

This invention relates to novel 1-(4-acylamino-phenyl)-
-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives of the
general formula (I),

10



(I)

15

wherein

R stands for hydrogen or a C₁₋₄ alkyl group optionally
substituted by a carboxyl or C₂₋₅ alkoxy-carbonyl group;
and

R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl
group,

as well as their acid-addition salts and pharmaceutical
compositions containing these compounds.

Due to the asymmetric C-4 carbon atom, the compounds of
the general formula (I) can exist in the form of optically
active enantiomers. The invention also relates to the race-

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mates, pure individual enantiomers and any mixture thereof.

According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I) and acid addition salts thereof.

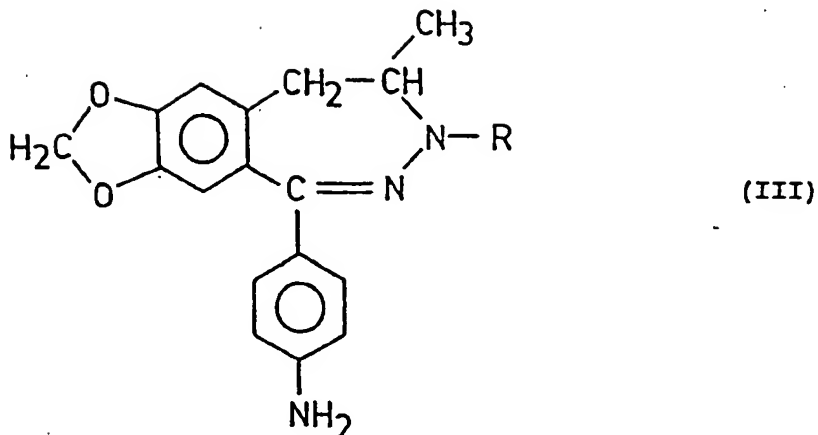
5 The aim of the present invention is to provide novel 5H-2,3-benzodiazepine derivatives possessing valuable central nervous system (CNS) effects, namely antidepressive and/or antiparkinsonian action, i.e. showing CNS-stimulating character and more advantageous properties than the 1-(4-
10 -aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see United States patent specification No. 4,835,152), the single 5H-2,3-benzodiazepine derivative known in this therapeutic area.

Now it has been found that the compounds of general
15 formula (I) and their acid-addition salts entirely satisfy the above demands since their effectivity reaches that of the known compound mentioned above and, in opposition to the above compound, they proved to be non-mutagenic in the Ames-test.

20 According to the invention, the novel compounds of general formula (I) are prepared by
a₁) transforming a compound of the general formula (III)

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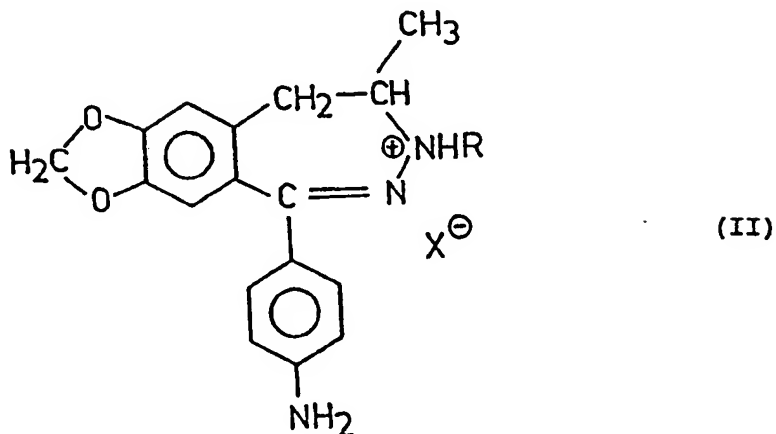
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wherein R is as defined above, to a compound of the general formula (II),

15



20

wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, by using an organic or inorganic acid, then acylating the product obtained, optionally without separating it, with a $\text{C}_1\text{-6}$ aliphatic carboxylic acid, benzoic or phenylacetic acid or a reactive derivative of these acids; or

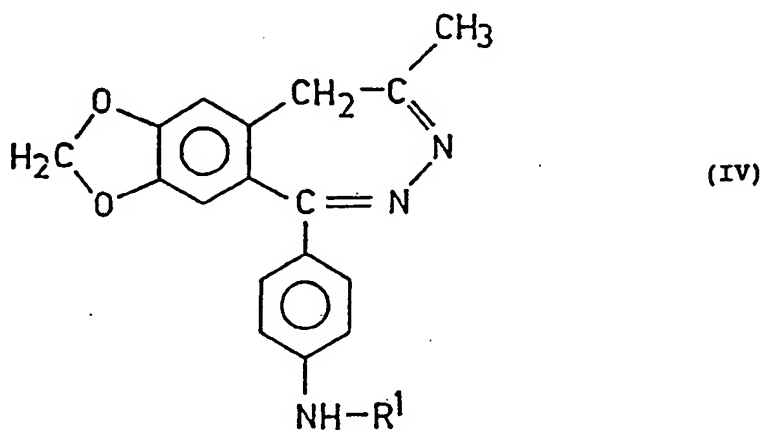
a₂) acylating a compound of the general formula (II),

25

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wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, with a C₁₋₆ aliphatic carboxylic, benzoic or phenylacetic acid or a reactive derivative of these acids; or

5 b) reducing a compound of the general formula (IV),



wherein R¹ is as defined above, by using an inorganic or inorganic-organic complex metal hydride in a suitable solvent, to obtain compounds of the general formula (I), wherein R¹ is as defined above and R means hydrogen;

20 and, if desired, alkylating a compound of the general formula (I), wherein R¹ is as defined above and R stands for hydrogen, prepared by using any of the above processes a₁), a₂) or b), with a C₁₋₄ alkyl halide optionally substituted by a C₂₋₅ alkoxy carbonyl group or with a C₂₋₈ dialkyl sulfate in a

25 suitable solvent, in the presence of an acid-binding agent and/or, if desired, hydrolyzing and then treating with an acid a compound of the general formula (I), wherein R¹ is as defined above and R stands for a C₁₋₄ alkyl group substituted

by a C₂₋₅ alkoxy carbonyl group, to obtain a compound of the general formula (I), wherein R stands for C₁₋₄ alkyl substituted by a carboxyl group and/or, if desired, converting a compound of the general formula (I) thus obtained to an acid-addition salt or, conversely, transforming a salt obtained to the corresponding free base.

According to a preferred embodiment of the process of the invention, a compound of the general formula (III), wherein R is as defined above, is transformed to a salt by using an organic or inorganic acid and then the salt of the general formula (II) thus obtained, wherein R is as defined above and X represents an inorganic or organic anion, preferably chloride, bromide, hemisulfate or methanesulfonate anion, optionally without separation, is acylated with a C₁₋₆ aliphatic carboxylic, benzoic or phenylacetic acid or a reactive derivative of these acids.

In the salts of general formula (II), the quaternary nitrogen is present in the 7-membered cycle, therefore the aromatic primary amino group is free and can relatively readily be acylated. The acylation can be performed in a suitable solvent or in an excess of the acylating agent. It is particularly preferable to carry out the acylation in an excess of the carboxylic acid anhydride at a temperature between 10 °C and 50 °C. This reaction lasts in general 1 to 5 hours.

A preferred embodiment of preparing compounds of the general formula (I), wherein R¹ is as defined above and R means hydrogen, comprises reducing a compound of the general

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formula (IV), wherein R^1 is as defined above, by using an inorganic or inorganic-organic complex metal hydride in a suitable solvent. For this selective reduction e.g. lithium aluminum hydride, sodium borohydride, potassium borohydride, sodium borohydride-aluminum chloride, sodium cyanoboro-
5 sodium borohydride-aluminum chloride, sodium cyanoboro-
-hydride, sodium dihydro-bis(2-methoxyethoxy)-aluminate, lithium trimethoxyaluminum hydride or sodium borohydride-triethyloxonium fluoborate may be used as complex metal hydrides. It is suitable to carry out the reduction in water,
10 ethers, alcohols, aromatic hydrocarbons, pyridine or a mixture thereof. The use of solvents or solvent mixtures is defined by the reducing agent used in the given case: it should be chosen in such a way that it reacts with the reducing agent very slowly if at all.

15 According to a particularly advantageous embodiment of the process of the invention, sodium borohydride is used as complex metal hydride, pyridine is employed as solvent and the reduction is suitably carried out at a temperature between 50 °C and 115 °C.

20 According to the invention, compounds of the general formula (I), wherein R stands for C_{1-4} alkyl unsubstituted or substituted by a C_{2-5} alkoxycarbonyl group and R^1 is as defined above, can preferably be prepared also by alkylating a compound of the general formula (I), wherein R^1 is as
25 defined above and R represents hydrogen, with a C_{1-4} alkyl halide optionally substituted by a C_{2-5} alkoxycarbonyl group, or with a C_{2-8} dialkyl sulfate in a suitable solvent, preferably dimethylformamide or dimethylacetamide, in the presence

of an acid-binding agent such as e.g. an anhydrous alkali metal carbonate or hydrogen carbonate.

Free carboxylic acids can be obtained by the hydrolysis of esters, preferably by using an alkali metal hydroxide in 5 hot 50 % ethanol and liberating the carboxylic acid from its alkali metal salt thus obtained by using an acid, preferably acetic acid.

The transformation of bases of the general formula (I) to their acid-addition salts, suitably to pharmaceutically 10 acceptable acid-addition salts, is carried out in a known way, e.g. by dissolving or suspending the base in an appropriate solvent and adding the corresponding acid or its solution prepared in a suitable solvent. The salts are separated either directly by filtration or after evaporating the sol- 15 vent; if desired, the product obtained is suspended or recrystallized and/or dried under reduced pressure.

The preparation of the compounds of general formulae (II) and (III) (wherein R is hydrogen) used as starting substances in the process according to the invention is 20 published in the United States patent specification No. 4,835,152. The compounds of general formula (IV), wherein R¹ is as defined above, are new, and are described hereinafter in the Examples.

As mentioned in the introduction, the novel compounds 25 of general formula (I) prepared by the process according to the invention possess significant central nervous system effects.

The pharmacological activity of the compounds will

hereinafter be illustrated by results achieved in animal tests carried out by using mainly the compound of Example 1. In the comparative investigations 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

5 (hereinafter: reference compound; see the United States patent specification No. 4,835,152) was used as reference substance which exerts similar effects but it has proven to be positive in the Ames-test on the TA-98 Salmonella strain after activation.

10 1. The behavioural effects of the compounds according to the invention were evaluated on male CFLP mice with an average body weight of 20 g (see Table 1) after oral or intraperitoneal treatment, respectively, by using Irwin's method [Psychopharmacologia, 13, 222 (1968)].

15

Table 1

Behavioural effects in mice

	Compound (Example No.)	Doses (mg/kg)	
		100 i.p.	200 p.o.
20	Reference compound	SMA ↑ stereotypy	SMA ↑ stereotypy
	1	SMA ↑ stereotypy	SMA ↑ stereotypy
	2	transitory SMA ↓	φ
25	3	φ	φ
	4	φ	φ
	5	φ	φ

The number of animals was 5 in each group.

SMA: spontaneous motor activity;

↑ means increase; ↓ means decrease

φ: no symptom was observed

Based on the above results, behavioural effects being similar to those of the reference compound could be elicited 5 by using the compound of Example 1.

2. The effect of the compound of Example 1 on the
motility in mice was more precisely analysed by means of a
 motimeter functioning on the basis of the capacitive re-
 sistance principle. The measurement was immediately commenced
 10 after the treatment and lasted for 2 hours. The number of
 animals was at least 12 in each group. The percentage changes
 determined from the total counts during 2 hours in relation
 to the vehicle as control are shown in Table 2. The signifi-
 cance was calculated from the number of counts by using
 15 Duncan's test.

Table 2

Effect on the motility in mice

Treatment		Doses (mg/kg) i.p.	Change %	Significance
20	Reference compound	3	+2.8	N.S.
		10	+90.6	p<0.01
		30	+318.7	p<0.01
25	Compound of Example 1	5	+8.0	N.S.
		10	+57.8	p<0.05
		20	+69.3	p<0.05
		30	+317.3	p<0.02

N.S.: not significant

It is obvious from the data of Table 2 that the moti-
 lity of mice was similarly increased both by the reference
 compound and the compound of Example 1.

3. Investigation into the antidepressive effect in rodents

3.1. Antagonization of reserpine hypothermia in mice

These examinations were performed in male CFLP mice by using an Ellab thermometer (measurement of the rectal temperature) by the method of Askew [Life Sci. 2, 725 (1963)].

The effects of the reference compound and the compound of Example 1 are shown in Table 3. The measurement was commenced after the treatment by the test substances.

Table 3

Antagonization of reserpine hypothermia in mice

Treatment	Doses (mg/kg)	Difference in the body temperature in relation to the reserpine control (°C)							
		p.o.	after						
			0	1	2	3	4	5	6 hours
Vehicle	-		+5.0	+7.7	+6.7	+5.9	+4.9	+4.6	+4.7
Reference	25		-0.3	+3.5**	+3.7**	+3.1**	+2.2**	+1.7**	+1.4**
20 compound	50		-0.2	+5.5**	+4.9**	+4.0**	+2.9**	+2.6**	+2.3**
Vehicle	-		+5.4	+5.3	+3.5	+2.9	+3.0	+2.5	+1.9
Compound	25		-0.3	-0.9	+1.3	+2.0**	+1.7**	+0.9	+0.8
of	50		-1.5*	0	+1.1	+2.5**	+1.8**	+1.5**	+0.5
25 Example 1	100		-1.8*	+0.5	+2.6**	+4.0**	+4.1**	+2.3**	+1.2

*: $p < 0.05$

** : $p < 0.01$.

The hypothermic effect of reserpine was significantly antagonized by both molecules.

3.2. Porsolt's test in rats

The escape-directed fight-strengthening effects of the reference compound and the compound of Example 1 in a state of despair were investigated in male OFA rats by using Porsolt's method [Eur. J. Pharmacol. 47, 379 (1978)]. The pre-selected animals were orally treated 3 times (24, 5 and 2 hours, respectively, before the measurement) with the compounds (see Table 4).

Table 4

10 Antidepressive effect in rats (Porsolt's test)

	Treatment	Dose (mg/kg)	Increase in the fighting time	Significance*
		p.o.		
15	Vehicle	-	-	-
	Reference	10	61.6 %	p < 0.05
	compound	30	159.5 %	p < 0.01
	Vehicle	-	-	-
	Compound of	3	40.3 %	p < 0.05
20	Example 1	10	66.8 %	p < 0.05
		30	110.2 %	p < 0.01

*: Calculated from the fighting time by using Duncan's test (R.G.D. Steel and J.H. Tonie: Principles and Procedures of Statistics, 2nd Edition, p. 187, McGraw-Hill Book Co.)

25

The compound of Example 1 exerted in this test an anti-depressive effect being similar to that of the reference compound: it resulted in a significant escape-directed fight-strengthening effect even in an oral dose of 3 mg/kg.

4. Anti-parkinsonian effect in mice [inhibition of the neurotoxicity of N-methyl-4-phenyltetrahydropyridine (abbreviated: MPTP)]

These examinations were carried out in male C57 mice 5 with an average body weight of 25 g by using the method of Mayer et al. [J. Neurochem. 47, 1073 (1986)].

This measurement is based on the fact that MPTP, more particularly the MPP^+ ion arising from MPTP through an enzymatic way catalyzed by MAO-B and getting into the neuron 10 via the dopamine-uptake system, leads to the destruction of dopaminergic cells. Thus, a status being similar to the Parkinson's disease can experimentally be established. This process can be prevented by compounds showing an anti-parkinsonian action.

15 The effect of the reference compound and compound of Example 1 are summarized in Table 5.

Table 5

Inhibition of the MPTP neurotoxicity in mice

20	Time of administration of compounds in relation to the treatment with MPTP (hour)	Reference compound Relative effect (%) $\bar{X} \pm S.E.$	N	Compound of Example 1 Relative effect (%) $\bar{X} \pm S.E.$	N
25	-4	-8 ± 2.6	9	1 ± 4.2	6
	-2	18 ± 16	4	8 ± 3.5	6
	-1	28 ± 12	3	$20 \pm 4^*$	6
	-0.5	$32 \pm 6^*$	12	$37 \pm 2.8^*$	12
	+0.5	$61 \pm 4^*$	11	$55 \pm 6^*$	6
	+1	$61 \pm 4^*$	11	$42 \pm 4.2^*$	10
	+2	$43 \pm 5^*$	12	$25 \pm 5.2^*$	4
	+4	$19 \pm 4^*$	17	11 ± 3.4	11
	+6	6 ± 1.8	12	1 ± 1.3	6

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*: Significant difference in relation to the MPTP control

N: number of animals

Doses: 2 x 30 mg/kg i.p.

$$\text{Relative effect (\%)} = \frac{\text{DA level}_{(\text{MPTP+compound})} - \text{DA level}_{(\text{MPTP})}}{100 - \text{DA level}_{(\text{MPTP})}} \times 100$$

DA: dopamine

According to the data of Table 5 both the reference compound and the compound of Example 1 significantly reduce the dopamine-level decrease induced by the treatment with MPTP. This effect of both compounds appear under the effect of treatments both before and after administration of MPTP.

Biochemical investigations were carried out in order to elucidate the action mechanism functioning in the anti-depressive and anti-parkinsonian as well as stimulatory effects of the compound of Example 1 and appearing in the pharmacological investigations.

The direct dopamine receptor-binding studies gave negative results.

5. Inhibition of the dopamine and MPP⁺ uptake

These examinations were carried out on a raw synaptosome preparation from the striatal tissue of the rat brain according to Schacht and Hepter [Biochem. Pharmacol 12, 3412 (1974)] or Javitch and Snyder [Eur. J. Pharmacol. 106, 455 (1985)], respectively. The results are summarized in Table 6.

Table 6

The in vitro inhibition of dopamine and MPP⁺ uptake

Compound	IC ₅₀ (M)	
	Dopamine	MPP ⁺
Reference compound	7.6 x 10 ⁻⁶	2.8 x 10 ⁻⁶
Compound of Example 1	8.3 x 10 ⁻⁶	8.8 x 10 ⁻⁶

10

The reference compound and the compound of Example 1 inhibit the dopamine and MPP⁺ uptake into the neuron with the same effectivity. The pharmacological activity can be explained by this biochemical effect.

15 6. Other central nervous system effects

These measurements were performed in male CFLP mice with a body weight of 20 g.

For the examination of the narcosis-potentiating effect, the animals were orally treated with the test substances and 30 minutes later they received an intravenous dose of 50 mg/kg of hexobarbital inducing narcosis. The prolongation of the duration of narcosis was measured in relation to the vehicle control group.

For investigation of the anticonvulsive effect, a tonic-clonic seizure was induced by electric current (10 mA, 2 sec, 0.4 msec) after 1-hour oral pretreatment. The ceasing of tonic extension of the hind legs was evaluated as an anticonvulsive effect [Swinyard: J. Pharm. Exp. Ther. 106, 319

(1952)]. The results are summarized in Table 7.

Table 7

Other central nervous system effects on mice

Compound	Anticonvulsive effect (ES) oral ED ₅₀ * (mg/kg)	Narcosis-potentiating effect after an oral dose of 50 mg/kg
5	Reference compound	52
		479 %
		(39.7-68.1)
10	1	195
		68 %
		(159.8-237.9)
	2	98
		159 %
		(77.8-123.5)
	3	> 100
		232 %
15	4	> 100
		159 %
	5	> 100
		152 %

*: Calculated by using probit analysis

ES: electric seizure (electroshock)

20 None of the tested molecules reached the anticonvulsive and narcosis-potentiating effect of the reference compound; however, the compounds of Examples 1 and 2 showed a considerable activity in the anticonvulsive test.

7. Acute toxicity in mice

25 The approximating LD₅₀ values of the compound of Example 1 (after a single treatment with an observation period of 14 days) are as follows:

Oral LD₅₀: > 500 mg/kg

Intraperitoneal LD₅₀: ≈ 150 mg/kg

Summing up, it can be stated that, among the compounds according to the invention, the compound of Example 1 shows

in rodents an antidepressive and anti-parkinsonian effect of the same order as the reference compound. The mechanism of action of both molecules is the same: they selectively inhibit the dopamine uptake (and simultaneously the MPP⁺) 5 system.

Considering that cerebral depaminergic systems play an actual and essential role in the motivated behaviour, it may be hoped that molecules acting on this system would show a considerable antidepressive effect in man. This supposition 10 is supported by several drug candidates possessing a similar biochemical mechanism of action with a positive effect in man, such as e.g. bupropion [chemically (±)-2-tert-butyl-amino-3'-chloropropiophenone hydrochloride] or amineptine [chemically 7-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5- 15 -yl)aminoheptenoic acid hydrochloride].

On the other hand, the advantageous effect in the MPTP model of the compound of Example 1, which is similar to that of the reference compound (MPTP induces Parkinson's disease in man, too), indicates the possibility of a human anti-par- 20 kinsonian effectivity.

On the basis of the above pharmacological results, the compounds of the invention can be used for treating depressive conditions and parkinsonism.

For therapeutical use, an indicated oral daily dose is 25 in the range from about 0.05 mg/kg to about 20 mg/kg, preferably from 0.1 mg/kg to 10 mg/kg, more preferably 1 mg/kg.

For therapeutical use, the active compounds of the invention are suitably formulated to pharmaceutical composi-

tions by mixing them with nontoxic, inert solid or liquid carriers and/or additives, which are suitable for enteral or parenteral administration and are commonly used in the pharmaceutical industry. Suitable carriers are e.g. water, 5 gelatin, lactose, starch, pectin, magnesium stearate, stearic acid, talc and vegetable oils. As additives preservatives, wetting (surface-active), emulsifying or dispersing, buffering and aromatizing agents may be used.

By using the above carriers and additives, the active 10 compounds of the invention may be formulated to the usual pharmaceutical compositions, e.g. solid forms (such as mainly tablets, dragées and capsules) as well as to injectable solutions, suspensions and emulsions.

The invention also relates to pharmaceutical 15 compositions containing a compound of the general formula (I) or a pharmaceutically acceptable acid-addition salt thereof as active ingredient as well as to a process for preparing these compositions.

The compositions according to the invention can be 20 prepared by commonly known methods.

The invention also relates to a method for treating depressive illnesses and Parkinson's disease. This method comprises administering a therapeutically effective amount of an active ingredient of the general formula (I) to the 25 patient in need of such treatment.

The identification of compounds of the invention was performed by elementary analysis; their purity and structure were proven by thin-layer chromatography (TLC) as well as by

their IR, ¹H-NMR and mass spectra. The data of analysis were in accordance with the empirical formula within the limits of error.

The invention is further illustrated by the following 5 non-limiting Examples.

Example 1

1-(4-Acetylamino-phenyl)-4-methyl-7,8-methylenedioxy-
-3,4-dihydro-5H-2,3-benzodiazepine

Method A)

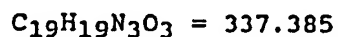
10 To a solution containing 6.0 g (20 mmol) of 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (see United States patent specification No. 4,835,152) in 30 ml of ethyl acetate 1.38 ml (21 mmol) of methanesulfonic acid were added. The crystalline precipitate
15 was filtered and washed with 5 x 5 ml of ethyl acetate. The dry weight of the product was 7.37 g, m.p.: it sintered above 190 °C and weakly decomposed at 210-212 °C. The thus-obtained methanesulfonate salt of the starting substance could be acetylated as follows:

20 7.37 g of the powdered salt were suspended in 110 ml of acetic anhydride, the suspension was stirred at room temperature for 2 hours, then the crystalline precipitate was filtered, washed with 5 x 10 ml of ethyl acetate and dried to give 6.54 g of methanesulfonate salt of the target compound,
25 m.p. 240-241 °C (with decomposition).

The base could be liberated from the methanesulfonate salt of the target compound e.g. in the following way: 6.54 g of salt were dissolved in 90 ml of water, the solution was

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clarified by charcoal, then 3.6 g of sodium hydrogen carbonate were portionwise added to the clear solution. The precipitate was filtered, washed with 5 x 10 ml of water and dried to obtain 5.54 g of crude product. After recrystallization from 130 ml of isopropanol, 3.11 g (yield 46 %) of product were obtained, m.p.: 221-223 °C (weak decomposition), the melting point of which was increased to 223-225 °C after digesting with 15 ml of hot benzene.



10 The hydrochloride salt decomposed at 262-264 °C.

Method B)

After dissolving 15.0 g (44.7 mmol) of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 150 ml of pyridine under mild heating, 10.2 g (0.269 mol) of sodium borohydride were added and the mixture was stirred on an oil bath of 100 °C temperature for 5 hours. Then the reaction mixture was cooled to about 25 °C, 150 ml of water were dropwise added under continuous stirring during 20 minutes, thereafter a mixture containing 180 ml of concentrated hydrochloric acid and 265 ml of water was added while cooling by ice-water. A yellowish suspension was formed. The precipitate was filtered, washed with 5 x 20 ml of water and dried to yield 15.2 g of salt, m.p. above 250 °C. In order to liberate the base, this salt was suspended in 150 ml of 50 % ethanol, 5.7 g of sodium hydrogen carbonate were portionwise added while stirring, then the suspension was filtered after 30 minutes, washed successively with 3 x 10 ml of 50 % ethanol, with 5 x 20 ml of water, finally

with 20 ml of 50 % ethanol and dried to obtain 10.95 g of a crude product, m.p.: 218-220 °C (weak decomposition). After digesting this crude product with 50 ml of hot isopropanol and then with 100 ml of hot 99.5 % ethanol, 8.63 g (57.2 %) of the aimed compound were obtained, m.p.: 220-222 °C (weak decomposition).

The starting substance was prepared as follows.

10 g (34 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine were stirred for 3 hours with 100 ml of acetic anhydride. The crystals formed were filtered, washed with 5x10 ml of anhydrous ethanol and dried, to yield 9.2 g of raw product, m.p.: 252-254 °C (decomposition). This product was treated with 45 ml of hot 99.5 % ethanol. After cooling the crystals were filtered, washed with 3x10 ml of ethanol and dried to obtain 8.68 g (76.1 %) of 1-(4-acetylamino-phenyl)-4-methyl-7,8-methylene-dioxy-5H-2,3-benzodiazepine, m.p.: 256-258 °C.

$C_{19}H_{17}N_3O_3 = 335.369$

Example 2

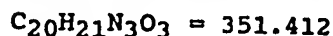
20 1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

Method A)

After adding 1.70 g (4.3 mmol) of powdered 1-(4-amino-phenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine methanesulfonate to 10 ml of propionic acid anhydride, the reaction mixture was stirred at 20 °C for 2.5 hours. The precipitated salt was washed with 4 x 5 ml of ethyl acetate and dried to give 1.86 g of product, m.p.:

246-248 °C (decomposition). The base was liberated as described in Method A) of Example 1 to obtain 1.36 g of product, m.p.: 226-233 °C (weak decomposition). The melting point of this product was increased to 237-239 °C after re-

5 crystallization from 40 ml of 99.5 % ethanol to give the aimed compound in a yield of 1.8 g (71.5 %).



The same product was obtained with a yield of 65 % by adding first 2.15 mmol of concentrated sulfuric acid, then

10 4.3 mmol of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine base to the propionic acid anhydride and otherwise working as described above.

Method B)

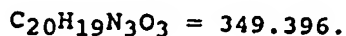
When starting from 1.65 g (4.72 mmol) of 1-(4-

15 -propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine and otherwise following Method B) of Example 1 (except that alkalization was carried out by using 40 % aqueous sodium hydroxide solution and the extraction was performed by using benzene) and recrystallizing the crude

20 product from ethanol, 1.2 g (72.3 %) of the aimed product were obtained, m.p.: 235-236 °C (weak decomposition).

1-(4-Propionylaminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine used as starting substance was prepared in the same way as described above for the 4-acetyl-

25 amino analogue, except that propionic acid anhydride was used instead of acetic acid anhydride, m.p.: 228-230 °C (decomposition).



Examples 3 to 5

The compounds of Examples 3 to 5 were also prepared as described in Method B) of Example 1.

Example 3

5 1-(4-Benzoylamino-phenyl)-4-methyl-7,8-methylenedioxy-
-3,4-dihydro-5H-2,3-benzodiazepine

$C_{24}H_{21}N_3O_3 = 399.456$; it decomposes at 247-248 °C.

The 1-(4-benzoylamino-phenyl)-4-methyl-7,8-methylene-
dioxy-5H-2,3-benzodiazepine used as starting substance was
10 obtained as follows.

1.0 ml (15 mmol) of benzoyl chloride and 2.1 ml (15
mmol) of triethylamine were added to a solution of 4 g (13.6
mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-
-2,3-benzodiazepine in dichloromethane and the reaction
15 mixture was stirred at 25 °C for 24 hours. The solution was
extracted with 3x30 ml of water, 3x20 ml of a 4 % aqueous
sodium hydroxide solution and finally with 2x30 ml of
distilled water. The organic layer was dried, evaporated at
reduced pressure, then the crystalline residue was treated
20 with 20 ml of hot ethanol to yield 3.97 g of raw product,
m.p.: 242-243 °C. This raw product was repeatedly treated
with 20 ml of hot ethanol, next day it was filtered at 0-5
°C, washed with 3x3 ml of ethanol and dried at 100 °C to
obtain 3.85 g (71.3%) of a pure product, m.p.: 246-247 °C
25 (decomposition).

$C_{24}H_{19}N_3O_3 = 397.40$

Example 4

4-Methyl-7,8-methylenedioxy-1-(4-phenylacetyl-amino-phenyl)-3,4-dihydro-5H-2,3-benzodiazepine

$C_{25}H_{23}N_3O_3 = 413.483$; it decomposes at 213-215 °C.

5 The 4-methyl-7,8-methylenedioxy-1-(4-phenylacetyl-amino-phenyl)-5H-2,3-benzodiazepine used as starting substance was prepared in the following way.

After adding 0.7 g (3.4 mmol) of DCC and 0.46 g (3.4 mmol) of phenylacetic acid to the solution of 0.5 g (1.7 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 30 ml of anhydrous methylene chloride, the mixture was stirred at 25 °C for 48 hours and filtered. The precipitate was combined with the evaporation residue of the filtrate and purified by chromatography on silica gel, by using a 4:1 mixture of ethyl acetate-methanol as eluent. The fractions containing the aimed product were evaporated, the residue was boiled with 5 ml of ethanol, cooled down and filtered to obtain 0.60 g (87.72 %) of the aimed product, m.p.: 245-247 °C (decomposition).

20 Example 5

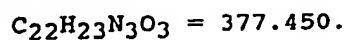
4-Methyl-7,8-methylenedioxy-1-(4-pivaloylamino-phenyl)-3,4-dihydro-5H-2,3-benzodiazepine

$C_{22}H_{25}N_3O_3 = 379.466$; it decomposes at 134-136 °C.

The 4-methyl-7,8-methylenedioxy-1-(4-pivaloylamino-phenyl)-5H-2,3-benzodiazepine used as starting substance was prepared in the following manner.

1.56 ml (11.2 mmol) of triethylamine and 1.38 ml (11.2 mmol) of pivaloyl chloride were added to a solution of 3 g

(10.2 mmol) of 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine in 160 ml of dichloromethane and the reaction mixture was stirred at 25 °C for one hour. The precipitate formed was filtered, washed with 3x5 ml of dichloromethane, then with 3x20 ml of water and dried to give 1.59 g of the pure product, m.p. 225-227 °C (decomposition). The other portion of the product was isolated from the organic phase. The filtrate was extracted with 3x20 ml of water, then with 3x15 ml of 4 % aqueous sodium hydroxide solution, finally with 2x30 ml of water. The organic layer was subsequently dried and evaporated under reduced pressure. The crystalline residue was combined with the former 1.59 g of the product and suspended in 20 ml of hot ethanol. The product was filtered after cooling, washed with 3x3 ml of ethanol and dried to obtain 3.38 g (87.8 %) of the pure product, m.p.: 225-227 °C.

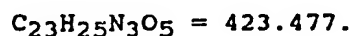


Example 6

1-(4-Acetylamino-phenyl)-3-ethoxycarbonylmethyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

1.26 g (3.7 mmol) of the target compound of Example 1 were dissolved in 5 ml of pure dimethylformamide, then 0.51 g (3.7 mmol) of potassium carbonate (anhydrous by heating) and 0.42 ml (3.7 mmol) of ethyl bromoacetate were added while stirring. The reaction mixture was stirred at room temperature for 6 hours. Next day the crude product was precipitated by adding 50 ml of water. After filtration, washing with

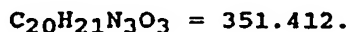
5 x 4 ml of water and drying, the crude product weighed 1.36 g. This product was purified by column chromatography on Kieselgel 60 by using a 4:1 ethyl acetate/benzene mixture for elution. After recrystallization from 10 ml of 50 % ethanol, 5 1.05 g (67 %) of the aimed product were obtained, m.p.: 156-157 °C.



Example 7

1-(4-Acetylamino-phenyl)-3,4-dimethyl-7,8-methylene-
10 dioxo-3,4-dihydro-5H-2,3-benzodiazepine

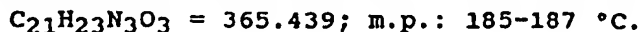
The process described in Example 6 was followed, except that methyl iodide was used instead of ethyl bromoacetate, the column chromatography was omitted and the crude product was recrystallized first from 50 % and then from 99.5 %
15 ethanol to give the pure aimed compound, m.p.: 207-209 °C.



Example 8

1-(4-Acetylamino-phenyl)-3-ethyl-4-methyl-7,8-methylene-
20 dioxo-3,4-dihydro-5H-2,3-benzodiazepine

The process described in Example 7 was followed, except that ethyl iodide was used instead of methyl iodide and the recrystallization was carried out with 50 % ethanol.

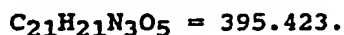


Example 9

25 1-(4-Acetylamino-phenyl)-3-carboxymethyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

0.59 g (1.4 mmol) of the compound of Example 6 was boiled with 15 ml of 50 % ethanol and 0.10 g (1.8 mmol) of

potassium hydroxide under reflux for 30 to 40 minutes. After cooling 0.15 ml (2.5 mmol) of acetic acid was added to the filtered, clear solution to liberate the free carboxylic acid which was then separated by filtration after cooling. The acid was washed with 4 x 2 ml of 50 % ethanol and then with 3 x 3 ml of water and dried to obtain 0.45 g (81.3 %) of the aimed product which sintered from 162 °C and weakly decomposed at 164-166 °C.



10 **Example 10**

Preparation of pharmaceutical compositions

a) Divided (grooved) tablets containing 25 mg of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine (compound of Example 1)

15 **Ingredients of one tablet:**

	Active ingredient	25.0 mg
	Magnesium stearate	0.5 mg
	Stearin	0.5 mg
	Talc	1.0 mg
20	Gelatin	1.7 mg
	Microcrystalline cellulose	5.0 mg
	Maize starch	10.3 mg
	Lactose	46.0 mg.

b) Dragées containing 12.5 mg of 1-(4-acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine

Ingredients of one dragée-core:

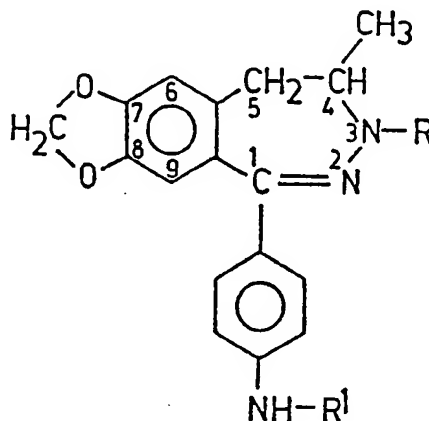
	Active ingredient	12.5 mg
	Magnesium stearate	1.0 mg
	Polyvinylpyrrolidone	5.0 mg
5	Maize starch	16.0 mg
	Lactose	38.0 mg.

The dragée-core was coated with sugar and talc in the usual way and then polished by using bee-wax. Each dragée weighed about 100 mg.

Claims

1. 1-(4-Acylaminophenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives of the general formula (I),

5



(I)

10

wherein

15 R stands for hydrogen or a C₁₋₄ alkyl group optionally substituted by a carboxyl or C₂₋₅ alkoxy carbonyl group; and

R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl group,

20 and their stereoisomers and acid-addition salts.

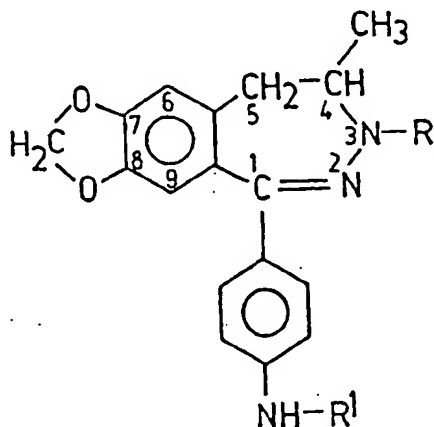
2. 1-(4-Acetylaminophenyl)-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine.

3. A pharmaceutical composition, which comprises as active ingredient a novel 1-(4-acylamino-phenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically acceptable acid-addition salt thereof in admixture with carriers and/or additives commonly

used in the pharmaceutical industry.

4. A process for the preparation of novel 1-(4-acylamino-phenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivatives of the general formula (I),

5



(I)

10

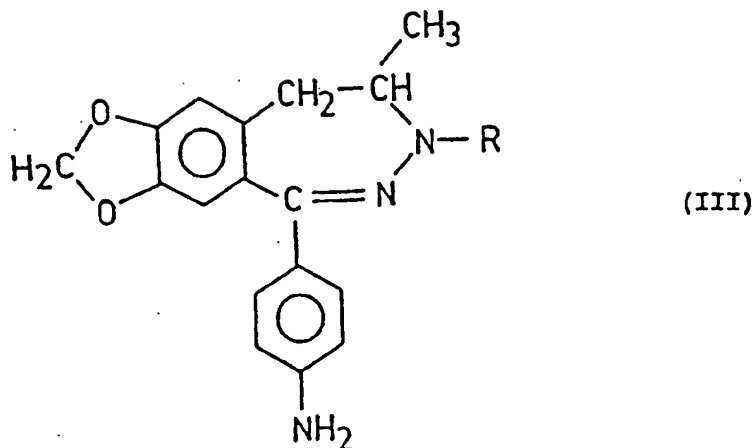
wherein

15 R stands for hydrogen or a C₁₋₄ alkyl group optionally substituted by a carboxyl or C₂₋₅ alkoxy-carbonyl group; and

R¹ means an aliphatic C₁₋₆ acyl, benzoyl or phenylacetyl group,

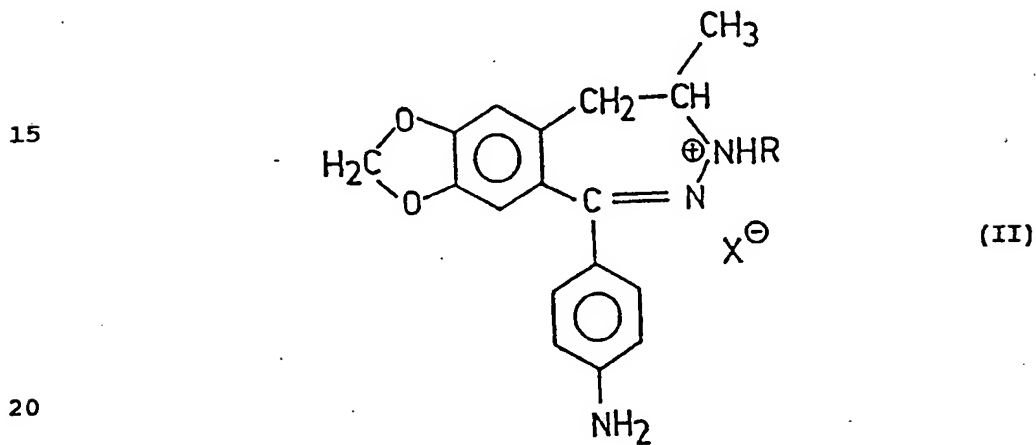
20 and their stereoisomers as well as acid-addition salts, which comprises

a₁) transforming a compound of the general formula (III)



10

wherein R is as defined above, to a compound of the general formula (II),



20

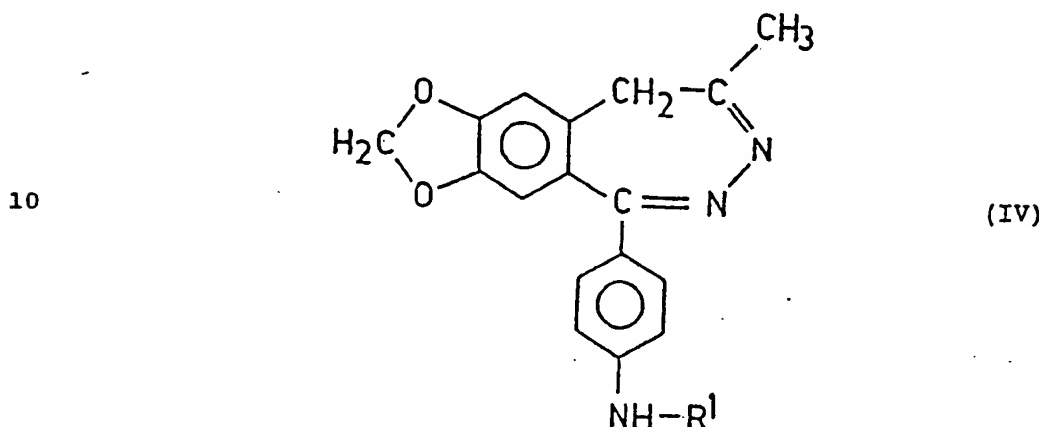
wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, by using an organic or inorganic acid, then acylating the product obtained, optionally without separating it, with a C₁₋₆ aliphatic carboxylic acid, benzoic or phenylacetic acid or a reactive derivative of these acids; or

25

a₂) acylating a compound of the general formula (II),

wherein R is as defined above and X means chloride, bromide, hemisulfate or methanesulfonate anion, with a C₁₋₆ aliphatic carboxylic, benzoic or phenylacetic acid or a reactive derivative of these acids; or

5 b) reducing a compound of the general formula (IV),



15

wherein R¹ is as defined above, by using an inorganic or inorganic-organic complex metal hydride in a suitable solvent, to obtain compounds of the general formula (I), wherein R¹ is as defined above and R means hydrogen;

20 and, if desired, alkylating a compound of the general formula (I), wherein R¹ is as defined above and R stands for hydrogen, prepared by using any of the above processes a₁), a₂) or b), with a C₁₋₄ alkyl halide optionally substituted by a C₂₋₅ alkoxycarbonyl group or with a C₂₋₈ dialkyl sulfate in a

25 suitable solvent, in the presence of an acid-binding agent and/or, if desired, hydrolyzing and then treating with an acid a compound of the general formula (I), wherein R¹ is as defined above and R stands for a C₁₋₄ alkyl group substituted

by a C₂₋₅ alkoxy carbonyl group, to obtain a compound of the general formula (I), wherein R stands for C₁₋₄ alkyl substituted by a carboxyl group and/or, if desired, converting a compound of the general formula (I) thus obtained to an acid-
5 addition salt or, conversely, transforming a salt obtained to the corresponding free base.

5. A process as claimed in claim 4, process a₁) or a₂), which comprises carrying out the acylation with the corresponding carboxylic acid anhydride, preferably in an
10 excess of the carboxylic acid anhydride, at a temperature between 10 °C and 50 °C during 1 to 5 hours.

6. A process as claimed in claim 4, process b), which comprises using lithium aluminum hydride, sodium borohydride, potassium borohydride, sodium borohydride/aluminum chloride,
15 sodium cyanoborohydride, sodium bis(2-methoxyethoxy)aluminum hydride, lithium trimethoxyaluminum hydride or sodium borohydride/triethyloxonium fluoborate and carrying out the reduction in a solvent or solvent mixture which is non-reacting or slowly reacting to the complex metal hydride employed.

20 7. A process as claimed in claim 6, which comprises carrying out the reduction with sodium borohydride in pyridine.

8. A process as claimed in claim 4, which comprises carrying out the alkylation in dimethylformamide, in the
25 presence of an anhydrous alkali metal hydrogen carbonate or carbonate as acid-binding agent.

9. A process as claimed in claim 4, which comprises carrying out the selective hydrolysis of compounds of the

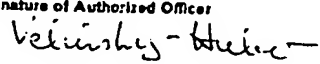
general formula (I), containing as R a C₁₋₄ alkyl group substituted by a C₂₋₅ alkoxy carbonyl group, by using an alkali metal hydroxide in hot 50 % ethanol and liberating the free carboxylic acid derivative by acetic acid.

5 10. A process for the preparation of a pharmaceutical preparation, which comprises mixing as active ingredient a novel 1-(4-acylamino phenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically
10 acceptable acid-addition salt thereof, prepared by using any of processes a₁) to b) claimed in claim 4, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

11. Method for treating mammals (including man)
15 suffering from a depressive illness or Parkinson's disease, which comprises administering a therapeutically effective amount of an 1-(4-acylamino phenyl)-7,8-methylenedioxy-5H-2,3-benzodiazepine derivative of the general formula (I), wherein R and R¹ are as defined in claim 1, or a pharmaceutically
20 acceptable acid-addition salt thereof, to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00053

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. ⁵ : C 07 D 491/056 // (C 07 D 491/056, 317:00, 243:00)						
II. FIELDS SEARCHED Minimum Documentation Searched ⁷ : <table border="1"> <tr> <th>Classification System</th> <th>Classification Symbols</th> </tr> <tr> <td>Int.Cl. ⁵</td> <td>C 07 D 491/056</td> </tr> </table>			Classification System	Classification Symbols	Int.Cl. ⁵	C 07 D 491/056
Classification System	Classification Symbols					
Int.Cl. ⁵	C 07 D 491/056					
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸ : AT						
III. DOCUMENTS CONSIDERED TO BE RELEVANT						
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³				
D, A	US, A, 4 835 152 (KORÖSI et al.) 30 May 1989 (30.05.89), see claims 1-7.	1-4, 10				
A	US, A, 4 423 044 (KORÖSI et al.) 27 December 1983 (27.12.83), see abstract.	1				
<p>* Special categories of cited documents: ¹⁴</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search 25 March 1992 (25.03.92)		Date of Mailing of this International Search Report 01 April 1992 (01.04.92)				
International Searching Authority AUSTRIAN PATENT OFFICE		Signature of Authorized Officer 				

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 11 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers _____ because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____ because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANHANG

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

ANNEX

to the International Search
Report to the International Patent
Application No.

ANNEXE

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

PCT/HU91/00053

In diesem Anhang sind die Mitglieder
der Patentfamilien der im obenge-
nannten internationalen Recherchenbericht
angeführten Patentedokumente angegeben.
Diese Angaben dienen nur zur Unter-
richtung und erfolgen ohne Gewähr.

This Annex lists the patent family
members relating to the patent documents
cited in the above-mentioned inter-
national search report. The Office is
in no way liable for these particulars
which are given merely for the purpose
of information.

La présente annexe indique les
membres de la famille de brevets
relatifs aux documents de brevets cités
dans le rapport de recherche inter-
national visée ci-dessus. Les renseigne-
ments fournis sont donnés à titre indica-
tif et n'engagent pas la responsabilité
de l'Office.

Im Recherchenbericht angeführtes Patentedokument Patent document cited in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A	4835152	30-05-89	AU A1 76880/87	18-02-88
			AU B2 596206	26-04-90
			BE AE 1002415	05-02-91
			CA A1 1284322	21-05-91
			CH A 673652	30-03-90
			CS A2 8706007	16-08-88
			CS B2 264150	13-06-89
			DD A5 265627	08-03-89
			DE A1 3727226	18-02-88
			DK A0 4248/87	14-08-87
			DK A 4248/87	16-02-88
			ES AF 2004985	16-02-89
			FI A0 873525	14-08-87
			FI A 873525	16-02-88
			FI B 85706	14-02-92
			FR A1 2602773	19-02-88
			FR B1 2602773	02-11-90
			GB A0 8719265	23-09-87
			GB A1 2194236	02-03-88
			GB B2 2194236	21-03-90
			HU A2 47287	28-02-89
			HU B 198494	30-10-89
			IT A0 8721667	14-08-87
			JP A2 63099073	30-04-88
			NL A 8701909	01-03-88
			NO A0 873426	14-08-87
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			SE A 8703169	16-02-88
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